IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Phillips, J.O.	ATTORNEY DOCKET:	03117247
SERIAL NO.:	10/418,410	GROUP ART UNIT:	1614
FILED:	April 18, 2003	EXAMINER:	Unknown
TITLE:	Novel substituted benzimidazole dosage forms and method of using same		
DATE:	June 22, 2006	CUSTOMER NO.:	26565

Certificate of Mailing by "Express Mail"

"Express Mail" mailing label No. EV548617467US. Date of Deposit: June 22, 2006
I hereby certify that this paper (and its recited enclosures) or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop: Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

(signature of person mailing paper or fee)

Timothy M. Hubalik
(typed name of person mailing paper or fee)

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL LETTER

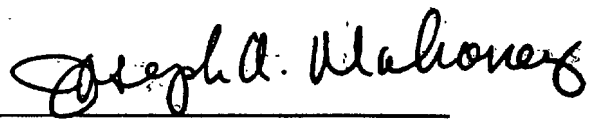
Dear Sir:

Enclosed herewith are the following for the above-captioned application:

1. Amendment and Response to Office Action dated December 23, 2005 and Petition for Extension of Time;
2. $1,080.00 check;
3. Exhibits 1-9; and
4. Return receipt postcard.

The Commissioner is hereby authorized to charge any additional filing fees required under Rule 1.17 concerning this transaction, or to credit any overpayment to Deposit Account 13-0019.

Respectfully submitted,



Joseph A. Mahoney
Reg. No. 38,956

Date: June 22, 2006

CUSTOMER NUMBER 26565
MAYER, BROWN, ROWE & MAW LLP
P.O. Box 2828
Chicago, Illinois 60690-2828
Telephone: (312) 701-8034
Facsimile: (312) 706-9000

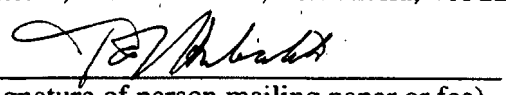
Docket No. 03117247

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Phillips, J.O.	ATTORNEY DOCKET:	03117247
SERIAL NO.:	10/418,410	GROUP ART UNIT:	1614
FILED:	April 18, 2003	EXAMINER:	Unknown
TITLE:	Novel Substituted Benzimidazole Dosage Forms and Methods of Using Same		
DATE:	June 22, 2006	CUSTOMER NO.:	26565

Certificate of Mailing by "Express Mail"

"Express Mail" mailing label No. EV548617467US. Date of Deposit: June 22, 2006. I hereby certify that this paper (and its recited enclosures) or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.



(signature of person mailing paper or fee)

Timothy M. Hubalik
(typed name of person mailing paper or fee)

Mail Stop: Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND RESPONSE TO OFFICE ACTION DATED DECEMBER 23, 2005

PETITION FOR EXTENSION OF TIME

This communication is responsive to the Office Action dated December 23, 2005. Applicant hereby petitions for an extension of time of three-months. In connection with this petition. please find payment in the amount of $1080 pursuant to 37 C.F.R. 1.17(a)(5). If any additional fee is deemed payable, please charge such a fee to Deposit Account No. 13-0019. Applicant respectfully requests entry of the proposed amendments and allowance of the pending claims.

Amendments to the claims begin on page 2.

Remarks/Arguments begin on page 8.

A **Conclusion** is on page 14.

IN THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application.

Listing of Claims:

1. (Currently Amended) A method for treating or preventing an acid-caused gastrointestinal disorder in a subject in need thereof, comprising orally administering to the subject a solid pharmaceutical composition comprising:

(a) a proton pump inhibitor selected from omeprazole, lanzoprazole, esomeprazole, pantoprazole, rabeprazole and pariprazole in an amount of about 2 mg to about 300 mg wherein at least some of the proton pump inhibitor is not enteric coated; and

(b) at least one primary essential buffer and at least one secondary essential buffer in a total amount of about 0.1 mEq to about 2.5 mEq per mg of proton pump inhibitor; wherein:

upon administration to the subject the proton pump inhibitor contacts stomach secretions; and the buffering agent is present in an amount sufficient to substantially prevent~~[[s]]~~ or inhibit acid degradation of at least a therapeutically effective amount of the proton pump inhibitor in the stomach secretions.

2. (Original) The method of claim 1, wherein the composition comprises an enteric coating.

3. (Original) The method of claim 1, wherein the composition comprises a film coating.

4. (Original) The method of claim 1, wherein the composition comprises a delayed-release coating.

5. (Original) The method of claim 1, wherein the proton pump inhibitor is in a homogeneous mixture with the buffering agent.

6. (Original) The method of claim 1, wherein the proton pump inhibitor is a substituted benzimidazole compound having H+, K+-ATPase inhibiting activity.

7. (Original) The method of claim 1, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole, pariprazole, and leminoprazole, or an enantiomer, isomer, free base, salt, or mixture thereof.

8. (Previously Presented) The method of claim 1, wherein the proton pump inhibitor is present in an amount of about 2 mg to about 120 mg.

9. (Cancelled)

10. (Cancelled)

11. (Cancelled)

12. (Previously Presented) The method of claim 1, wherein the proton pump inhibitor is present in an amount of about 2 mg, 10 mg, 15 mg, 20 mg, 30 mg, 40 mg, or 60 mg.

13. (Cancelled)

14. (Cancelled)

15. (Previously Presented) The method of claim 1, wherein the proton pump inhibitor is omeprazole or an enantiomer, isomer, free base, salt, or mixture thereof.

16. (Currently Amended) The method of claim 1, wherein the proton pump inhibitor is lansoprazole or an enantiomer, isomer, free base, salt, or mixture thereof.

17. (Cancelled)

18. (Previously Presented) The method of claim 1, wherein the proton pump inhibitor is esomeprazole or an enantiomer, isomer, free base salt, or mixture thereof.

19. (Cancelled)

20. (Cancelled)

21. (Cancelled)

22. (Currently amended) The method of claim 1, wherein the composition further comprises a binder, a flavoring agent, a sweetening agent, a disintegrant, a flow aid, a lubricant, an adjuvant, an antioxidant, a chelating agent, an isotonic agent, a thickening agent, a colorant, a diluent, a moistening agent, a preservative, a parietal cell activator, an antifoaming agent, a pharmaceutically compatible carrier, and mixtures thereof.

23. (Original) The method of claim 22, wherein the binder comprises crospovidone, microcrystalline cellulose, or a sugar.

24. (Original) The method of claim 22, wherein the flavoring agent comprises aspartame, dextrose, chocolate, vanilla, root beer, peppermint, spearmint, sucrose, cocoa, or watermelon.

25. (Original) The method of claim 22, wherein the disintegrant comprises croscarmellose sodium, a calcium, and sodium alginate complex, or sodium starch glycolate.

26. (Original) The method of claim 22, wherein the lubricant comprises magnesium stearate, calcium hydroxide, talc, or stearic acid.

27. (Original) The method of claim 22, wherein the diluent comprises lactose, corn starch, potato starch, or mannitol.

28. (Original) The method of claim 22, wherein the pharmaceutically compatible carrier comprises acacia, gelatin, colloidal silicon dioxide, calcium glycerophosphate, calcium lactate, maltodextrin, glycerine, magnesium silicate, sodium caseinate, soy lecithin, sodium chloride, tricalcium phosphate, dipotassium phosphate, sodium stearoyl lactylate, carrageenan, monoglyceride, diglyceride, or pregelatinized starch.

29. (Currently amended) The method of claim 1, wherein at least one of the primary essential buffer and the secondary essential buffer are independently selected from the group consisting of sodium bicarbonate, potassium bicarbonate, magnesium hydroxide, magnesium lactate, magnesium gluconate, magnesium oxide, magnesium aluminate, magnesium carbonate, magnesium silicate, aluminum hydroxide, potassium carbonate, potassium citrate, aluminum hydroxide/sodium bicarbonate coprecipitate, aluminum magnesium hydroxide, sodium citrate, sodium tartarate, sodium acetate, sodium carbonate, sodium polyphosphate, potassium polyphosphate, sodium pyrophosphate, potassium pyrophosphate, disodium hydrogenphosphate, dipotassium hydrogenphosphate, trisodium phosphate, tripotassium phosphate, sodium acetate, potassium metaphosphate, ~~magnesium carbonate, magnesium silicate,~~ calcium acetate, calcium glycerophosphate, calcium hydroxide, calcium lactate, calcium carbonate, and calcium gluconate, calcium bicarbonate, calcium citrate, sodium phosphate, and mixtures thereof.

30. (Previously Presented) The method of claim 1, wherein the primary essential buffer and the secondary essential buffer are present in a total amount of about 2 mEq to about 70 mEq.

31. (Previously Presented) The method of claim 1, wherein the primary essential buffer and the secondary essential buffer are present in a total amount of about 10 mEq to about 50 mEq.

32. (Cancelled)

33. (Previously Presented) The method of claim 1, wherein the primary essential buffer and the secondary essential buffer are present in a total amount of about 12.5 mEq to about 30 mEq.

34. (Cancelled)

35. (Original) The method of claim 29, wherein the primary essential buffer or the secondary essential buffer is sodium bicarbonate.

36. (Original) The method of claim 29, wherein the primary essential buffer or the secondary essential buffer is sodium carbonate.

37. (Original) The method of claim 29, wherein the primary essential buffer or the secondary essential buffer is calcium carbonate.

38. (Previously Presented) The method of claim 29, wherein the primary essential buffer or the secondary essential buffer is magnesium hydroxide.

39. (Previously Presented) The method of claim 29, wherein the primary essential buffer is sodium bicarbonate and the secondary essential buffer are independently selected from sodium carbonate, calcium carbonate, magnesium hydroxide, and magnesium oxide.

40. (Original) The method of claim 1, wherein the amount of the primary essential buffer or the secondary essential buffer is more than about 40 times the amount of the proton pump inhibitor on a weight to weight basis in the composition.

41. (Original) The method of claim 1, wherein the proton pump inhibitor is micronized.

42. (Previously presented) The method of claim 1, wherein at least one of the primary essential buffer or the secondary essential buffer is micronized.

43. (Original) The method of claim 1, wherein the solid pharmaceutical composition is in a form of a tablet, a capsule, a powder, a pellet, a granule, or a troche.

44. (Original) The method of claim 43, wherein the tablet is a suspension tablet, a chewable tablet, or an effervescent tablet.

45. (Original) The method of claim 43, wherein the powder is an effervescent powder.

46. (Original) The method of claim 43, wherein the powder is a powder for suspension.

47. (Original) The method of claim 46, wherein the powder is suspended in an aqueous medium before administration.

48. (Original) The method of claim 47, wherein the aqueous medium is selected from the group consisting of water, and sodium bicarbonate solution.

49. (Original) The method of claim 1, wherein the acid-caused gastrointestinal disorder comprises duodenal ulcer disease, gastric ulcer disease, gastroesophageal reflux disease, erosive esophagitis, poorly responsive symptomatic gastroesophageal reflux disease, pathological gastrointestinal hypersecretory disease, Zollinger Ellison Syndrome, or acid dyspepsia.

50. (Cancelled)

51. (Original) The method of claim 1, wherein the composition is administered to the subject once a day, or multiple times a day.

52. (Previously Presented) The method of claim 1, wherein at least one of the primary essential buffer and the secondary essential buffer are independently selected from the group consisting of a calcium buffering agent, a magnesium buffering agent, an aluminum buffering agent, a sodium buffering agent, a bicarbonate salt of a Group IA metal, an alkaline earth metal buffering agent, or mixtures thereof.

REMARKS

By the present amendment, three (3) claims are amended. No fees for claims are believed payable. Claims 1 – 8, 12, 15 – 16, 18, 22 – 31, 33, 35 – 49, and 51- 52 are presently pending.

Support for amended claim 1 can be found in the specification at least at paragraph 0058 on page 19 and paragraph 0053 on page 17. Amendments focus the presently claimed invention on certain embodiments and are made for reasons unrelated to patentability.

RESPONSE TO OFFICE ACTION DATED DECEMBER 23, 2005

1. The Rejection Under 35 U.S.C. § 112 Should Be Withdrawn

Claims 1 – 8, 12, 15 – 16, 18, 22 – 31, 33, 35 – 49, and 51- 52 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

The Examiner states that the "claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art to make and/or use the claimed invention. Applicant respectfully submits that this is not the standard for a *prima facie* case of lack of enablement. All that is necessary for enablement is that one of skill in the art be able to practice the claimed invention, given the level of knowledge and kill in the art. Not everything needed to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660 (Fed. Cir. 1991). Further, the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See *In re Fisher*, 427 F.2d 833 (CCPA 1970).

The Office Action indicates that the claims have not enabled a target population, but could apply to the population as a whole, and that such treatment may not be suitable for some subjects. Applicant respectfully submits that it is well within the capabilities of one of ordinary skill in the relevant art to determine which subjects have an "acid-caused gastrointestinal disorder" and which of those could benefit treatment according to the claimed invention. In short, one of ordinary skill in the art would be able to practice the claimed invention, given the level of knowledge in the art. Such is the proper standard for enablement. Because no *prima*

facie case of lack of enablement exists, Applicant respectfully requests withdrawal of this rejection.

2. Obviousness-Type Double Patenting

Claims 1-8, 12, 15-16, 18, 22—31,33,35-49 and 51-52 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over various claims of U.S. 6,699,885 as described in the Office Action. Applicant will submit a terminal disclaimer once allowable subject matter is indicated.

3. The Rejection Under 35 U.S.C. § 103 over EP 0584588 in view of Horowitz and Carroll Should Be Withdrawn

Claims 1-8, 12, 15-16, 18, 22—31, 33, 35-49 and 51-52 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over EP 0584588 (Nomura) in view of Horowitz and Carroll. Applicant traverses this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and both the suggestion and the expectation of success must be found in the prior art, not the applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988). As will be discussed in detail below, Applicant respectfully submits that in the instant case, no motivation exists to combine references as the Examiner proposes.

The claimed invention has distinct advantages over the Nomura, Horowitz, and Carroll references cited by the Examiner. Applicant and its exclusive licensee, Santarus, Inc., have generated data – and real-world clinical proof – demonstrating the advantages of the claimed invention over those in the references cited by the Examiner. The claimed invention has been approved by the FDA and is currently marketed in the United States by Santarus as Zegerid® Capsules and Powder for Oral Suspension. Referring to the Zegerid® Package Insert (attached as Exh. 1), the claimed invention not only provides 24 hour control of gastric acid, it also

provides immediate release of omeprazole and maximal blood levels within 30 minutes as compared to Prilosec®'s delayed-release mechanism (Exh. 2).

Moreover, as detailed below, none of the references cited by the Examiner render obvious Applicant's claimed invention. For example, with respect to one or more pending claims:

- The Examiner's apparent reliance on Horowitz and/or Carroll to illustrate that Nomura's compositions would provide a therapeutically effective amount of the proton pump inhibitor in the stomach secretions is misplaced
- There was no reasonable expectation at the time of the invention that the combination of references relied on by the Examiner would successfully result in the invention claimed by Applicant
- The references relied on by the Examiner fail to teach the motivation, desirability or interchangeability of their teachings
- The Examiner's suggestion that without any specific guidance the skilled person could pick and choose from the almost an infinite number of formulation possibilities presented in the references relied on by the Examiner to arrive at Applicant's claimed invention is random, speculative and based on the use of impermissible hindsight
- Even if combined, the references relied on by the Examiner, alone or in combination with one another, fail to teach or suggest each element of the claimed invention
- "Secondary considerations" confirm the non-obviousness of the claimed invention, e.g., proceeding contrary to accepted wisdom and license showing industry respect for the invention claimed.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. The burden of establishing a *prima facie* case of obviousness lies with the Examiner, and both the suggestion and the expectation of success must be found in the prior art, not the Applicant's disclosure." *In re Dow Chemical*, 5 USPQ 2d 1531 (Fed. Cir. 1988). Since there would have been no motivation to combine Carroll with Nomura in

such a manner as to arrive at the claimed invention, withdrawal of this rejection is respectfully requested.

Applicant respectfully submits that the combination of Carroll and Horowitz with Nomura is improper at least because Nomura teaches away from the combination of these two references. MPEP § 2146 clearly states that "[i]t is improper to combine references where the references teach away from their combination." *See In re Grasselli,* 713 F.2d 731 (Fed. Cir. 1983). Nomura teaches that the total basic material to total PPI ratio must be less than about 20:1, preferably between about 1.1:1 and 10:1, even more preferably between about 2.1:1 and 5:1. Nomura at p. 6, ll. 17-21. Specifically, "if the amount of basic material is too large, the administration of the composition is disturbed." *Id.* at p.6, ll. 20-21. Both Carroll and Horowitz, on the other hand, only disclose total buffering agent to total PPI weight ratios of greater than 20:1. As such, Nomura teaches away from any combination with Carroll or Horowitz, and no *prima facie* case of obviousness exists.

Furthermore, it is well settled that where a proposed combination would render one or more references inoperable for its intended purpose, the references are considered to teach away from their proposed combination and no motivation to combine exists. See MPEP §2143.01 V., and *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984). In this case, Carroll discloses the nasogastric administration of liquid compositions containing crushed enteric coated omeprazole granules which have been mixed with sodium bicarbonate solution. The purpose of the experiments described by Carroll was to overcome "difficulties with nasogastric tube delivery of omeprazole." However, Nomura is directed to compositions that are to be administered orally (not through a nasogastric tube; p. 6, ll. 28). The dosage forms disclosed by Nomura (tablets, pellets, capsules, powder, granules, syrup and paste) are not suitable for administration via a nasogastric tube because they would be too large and inflexible to fit down the lumen of a nasogastric tube or would plug the exit hole of the nasogastric tube, or in the case of a syrup would be so viscous as to clog the tube. *See, e.g.,* "Guidelines for the Management of Enteral Tube Feeding in Adults," (attached as Exh. 3) (published by the Clinical Resource Efficiency Support Team, April 2004), particularly page 51 indicating that viscous fluids such as syrups cause difficulties when administered down nasogastric tubes.

Therefore, the proposed combination of Carroll with Nomura would destroy the intended function of Carroll's composition—namely, nasogastric tube administration. As such, these references teach away from their combination and no *prima facie* case of obviousness exists.

It is also settled law that where a proposed combination would change the principles under which a reference was designed to operate, the teachings of the references are not sufficient to render the claims *prima facie* obvious. *See, e.g.,* MPEP §2143.01 VI.; *In re Ratti*, 7270 F.2d 810 (CCPA 1959). Because Nomura's compositions are stated to operate via oral delivery (*see* Nomura at p. 6, l. 28: "[t]he anti-ulcer composition according to the present invention is administered ***orally*** to human beings" (emphasis added)), and Carroll's method operates via nasogastric delivery, the combination of these references would impermissibly change the principle of operation of one or both references.

In addition, the Examiner's reliance on Horowitz as allegedly illustrating that at least a therapeutically effective amount of the proton pump inhibitor in Carroll's crushed enteric granules and/or Nomura's compositions would be available in the stomach secretions is misplaced for at least the following reasons.

As set forth in § 2131.01 III of the MPEP, in order to make a showing of inherency, the "***evidence*** must make clear that the missing descriptive matter is ***necessarily present*** in the thing described in the reference, and that it would be so recognized by persons of ordinary skill" (emphasis added). Horowitz is directed to *liquid, non-enteric coated* compositions. Nomura, on the other hand, is directed to *solid, enteric coated* compositions. As described above, Depui's dosage forms are enteric coated with a material that makes the PPI "insoluble in acidic media, but disintegrating/dissolving in near neutral to alkaline media such as, for instance the liquids present in the proximal part of the small intestine, where dissolution of the proton pump inhibitor is desired." Depui at p. 20, ll. 25-28. As such, the enteric coated PPI would not be available for absorption until after the enteric coated PPI passes through the stomach and enters the small intestine. Consequently, it is speculative at best to compare Depui's solid forms to Horowitz's liquid dosage forms.

Carroll teaches the delivery of an omeprazole suspension via a nasogastric tube and provides the following description for making the composition administered: (1) open the Prilosec® capsules containing enteric coated pellets, (2) crush the pellets, and (3) mix the *crushed enteric coated pellets* with 25 cc of sodium bicarbonate solution (1 mEq per ml).

Therefore, not only does Carroll fail to teach a powder containing both PPI and buffering agent, there is no evidence that Carroll's non-uniform slurry would naturally result in an a therapeutically effective amount of the proton pump inhibitor being available in the stomach secretions as claimed by Applicant. For example, if the composition was not sufficiently crushed, the enteric coating would still be intact and would likely prevent absorption of the PPI in the stomach thereby delaying the absorption of the PPI until sometime after it had passed through the stomach. In fact, Carroll itself suggests this by stating that the crushed enteric coated pellets are administered, indicating that enteric coating may still be intact on the PPI. Moreover, even if the enteric pellets were crushed, they would still need to be stirred in the bicarbonate solution for a sufficient period of time so as to allow the enteric coating to dissolve in order for the omeprazole to be available for absorption in the stomach. Carroll is silent as to any stirring step.

Additionally, as described in inventor Dr. Jeffery O. Phillips' Declaration (attached as Exh. 4), employing the Carroll method results in an undefined, non-homogeneous slurry rather than a uniform solution or suspension. Likewise, using crushed enteric coated pellets similar to the above does not appear to work:

> In one case, the omeprazole enteric-coated pellets had not completely broken down before the administration of the first two doses, which produced an erratic effect on gastric pH. The gastric pH increased to >5 as soon as the patient was given a dose of simplified omeprazole suspension (in which the enteric-coated pellets of omeprazole had been allowed to completely break down).

Phillips *et al.*, *"A Prospective Study of Simplified Omeprazole Suspension for the Prophylaxis of Stress-Related Mucosal Damage,"* Crit. Care Med. Vol. 24(ii): 1793-1800, 1795 (1996) (attached as Exh. 5).

Thus, Carroll's procedure prevents a finding of inherency because practicing this disclosure would not naturally result in "at least a therapeutically effective amount of the [non-enteric coated] proton pump inhibitor in the stomach secretions." *See Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 189 F.Supp. 2d 377 (Fed. Cir. 2002) ("A reference includes an inherent characteristic if that characteristic is the 'natural result' flowing from the reference's explicitly explicated limitations").

Moreover, it is well known that a given drug substance will have different absorption rates and times of onset depending on the dosage form and excipients, and that these differences are a function of both the formulation and the route of administration. *See e.g.* Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, Williams & Wilkins, 1995, pp. 77 (attached as Exh. 6). ("An individual drug substance may be formulated into multiple dosage forms which result in different drug absorption rates and times of onset, peak, and duration of action."). This is because, for example, a solid dosage form must first disintegrate and then dissolve before the PPI is released, and only after this occurs can the PPI be absorbed (assuming that it has not been degraded by stomach acid). Thus, Horowitz's liquid disclosure provides no meaningful evidence relevant to the performance of Nomura's compositions, and the Examiner's obviousness rejection should be withdrawn.

Although Applicant disagrees with any conclusion that a *prima facie* case of obviousness has been established for one or more of the above claims, Applicant submits herewith objective evidence of non-obviousness. Evidence rising from "secondary considerations" ***must always*** when present be considered en route to a determination of obviousness. MPEP § 716.01(a). Furthermore, "[a]ll of the competent rebuttal evidence ***taken as a whole*** should be weighed against the evidence supporting the *prima facie* case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984). (emphasis added).

Proceeding Contrary to Accepted Wisdom.

Proceeding contrary to accepted wisdom in the art is evidence of non-obviousness. *See In re Hegdes*, 783, F.2d 1038, (Fed. Cir. 1986). For example, in a 1996 reference by Herling et al., the authors state that "due to their inherent-chemical instability in acidic conditions, PPI's such as omeprazole, lansoprazole, etc. ***have to*** be administered orally as ***enteric coated formulations*** which prevent acidic degradation during passage through the stomach." Herling AW, Weidman K., *"Gastric proton pump inhibitors"* in Burgers' Medicinal Chemistry and Drug Discovery 1996: 119-151. *See also e.g., Astra Ag v. Andrx Pharmaceuticals, Inc.*, 222 F. Supp. 2d 423 (S.D.N.Y. 2002). ("Overcoming omeprazole's multiple sensitivities proved to be a substantial challenge, and Astra considered a number of different approaches to make an oral formulation") (attached as Exh. 7). Astra, therefore, concluded that the only commercially viable option was to enteric coat its product.

License Showing Industry Respect for Invention.

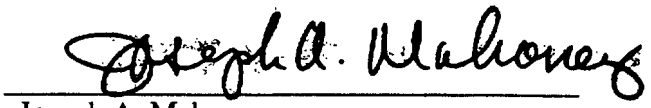
In addition, licenses showing industry respect for a claimed invention are objective evidence of non-obviousness. *Arkie Lures, Inc., v. Gene Larowe Tackle, Inc.*, 119 F.3d 953 (Fed. Cir. 1997) and *Pentec, Inc., v. Graphic Controls Corp.*, 776 F.2d 309 (Fed. Cir. 1985). In the present case, Applicant entered into a license agreement with Santarus, Inc., under which Santarus received the exclusive world-wide rights to make, use and sell, have made, have sold, offer for sale and import products under certain and future patent rights covering the invention, including rights under the instant patent. (Exh. 8). Pursuant to this license, Santarus has made significant expenditures related to the commercialization of its Zegerid® (omeprazole/sodium bicarbonate) products, which are covered by the '885 Patent. As part of its support for those activities, Santarus raised net proceeds of more than $80 million as a private company and net proceeds of more than $130 million in connection with its initial public offering and in subsequent financings. (Exh. 9). Zegerid® Capsules and Powder for Oral Suspension are presently marketed in the United States by Santarus.

For the foregoing reasons, Applicant submits that no *prima facie* case of obviousness has been established and respectfully requests withdrawal of this rejection.

Conclusion

All claims presented herein are believed to be in condition for allowance. Early and favorable consideration of this application is respectfully requested.

Respectfully submitted,



Joseph A. Mahoney
Registration No. 38,956

CUSTOMER NUMBER 26565
MAYER, BROWN, ROWE & MAW LLP
P.O. Box 2828
Chicago, IL 60690-2828
Telephone: (312) 701-8034
Facsimile: (312) 706-9000

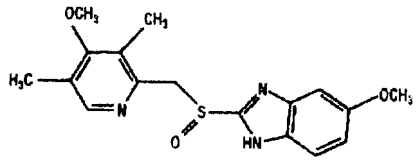
-Exhibits 1 – 9 attached

ZEGERID®
(omeprazole/sodium bicarbonate)

Rx only
Capsules
Powder for Oral Suspension

DESCRIPTION

ZEGERID® (omeprazole/sodium bicarbonate) is a combination of omeprazole, a proton-pump inhibitor, and sodium bicarbonate, an antacid. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole, a racemic mixture of two enantiomers that inhibits gastric acid secretion. Its empirical formula is $C_{17}H_{19}N_3O_3S$, with a molecular weight of 345.42. The structural formula is:



Omeprazole is a white to off-white crystalline powder which melts with decomposition at about 155°C. It is a weak base, freely soluble in ethanol and methanol, and slightly soluble in acetone and isopropanol and very slightly soluble in water. The stability of omeprazole is a function of pH; it is rapidly degraded in acid media, but has acceptable stability under alkaline conditions.

ZEGERID is supplied as immediate-release capsules and unit-dose packets as powder for oral suspension. Each capsule contains either 40 mg or 20 mg of omeprazole and 1100 mg of sodium bicarbonate with the following excipients: croscarmellose sodium and magnesium stearate. Packets of powder for oral suspension contain either 40 mg or 20 mg of omeprazole and 1680 mg of sodium bicarbonate with the following excipients: xylitol, sucrose, sucralose, xanthan gum, and flavorings.

CLINICAL PHARMACOLOGY

Omeprazole is acid labile and thus rapidly degraded by gastric acid. ZEGERID Capsules and Powder for Oral Suspension are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

Pharmacokinetics:

Absorption

In separate *in vivo* bioavailability studies, when ZEGERID Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of ZEGERID Powder for Oral Suspension (compared to I.V. administration) is about 30-40% at doses of 20 – 40 mg, due in large part to presystemic metabolism.